IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

ARMOUR et al. Atty. Ref.: 620-117; Confirmation No. 5675

Appl. No. 09/674,857 Group: 1644

Filed: November 7, 2000 Examiner: Huynh, P.

For: BINDING MOLECULES DERIVED FROM IMMUNOGLOBULINS WHICH DO NOT TRIGGER COMPLEMENT MEDIATED LYSIS

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January 26, 2004

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 181 PETITION

The applicants Petition the Commissioner to invoke his supervisory authority and have the restriction requirement of December 6, 2001, withdrawn, for at least the following reasons.

The Examiner has made the restriction requirement final. See, Office Action dated March 25, 2003 (Paper No. 22).

A Request for Continued Examination (RCE) is attached along with a separate Amendment in response to Paper No. 22, Information Disclosure Statement and Request for an interview with the Examiner prior to issuance of a further Action in the event either the restriction requirement is not withdrawn or the application as currently examined is not found to be in condition for allowance.

A favorable Decision on this Petition is requested.

The present invention is based on work in which the constant ("effector") regions of immunoglobulins were engineered in order to combine and manipulate their effector functions. As distinct from the prior art of record, this was done by multiple point mutations, in specific regions using only residues present in other immunoglobulins rather than using either (i) non-natural mutations, or (ii) wholesale grafting of regions. This has the advantage of producing molecules that are as 'natural' as possible, avoiding the introduction of potentially immunogenic regions, while also precisely controlling the effector functions which result. Such an approach has not been taken in any of the prior art of which Applicants are aware.

PCT Rules 13.I & 13.2:

All the claims and species have unity of the invention because they share a special technical relationship. The special technical feature which they share is the requirement that the binding molecules of all of claims 1 to 15 and 30:

(i) are capable of specifically binding FcγRIIb and optionally FcRn and,

(ii) and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4,

and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa and FcγRIII and a reduced ability to mediate complement lysis by comparison with said human immunoglobulin heavy chain CH2 domains

and wherein the chimeric domain is a human immunoglobulin heavy chain CH2 domain which has the following blocks of amino acids at the stated positions: 233P,

234V, 235A and no residue at 236 (or 236G); and 327G, 330S and 331S, numbered with respect to the EU system of Kabat and is at least 98% identical to a CH2 sequence (residues 231-340) from human IgG1 or IgG2 having said modified amino acids.

This combination of special technical features is not taught in the art, as further detailed below, and embodies a single general inventive concept that unifies the claims.

Claims 16-20 are based generally on nucleic acids that encode the instant binding molecules. The sequence of amino acids in the binding molecules described above is, of course, an essential structural element of those molecules, and it is encoded by an exactly corresponding sequence of codons in the nucleic acids. Thus, the same special technical features are found in these claims.

Claims 21-22 and 23-29 concern the production and use of the binding molecules of claim 32, or having the same special technical features of claim 32, thus they also have unity of invention.

All of these groups are technically related, and clearly fall within the meaning of the examples given in Annex B in the PCT administrative instructions, or in MPEP §1850.

The primers of claim 31 are novel and inventive by virtue of the fact that they are adapted for use in the claimed methods, and are in any case not suggested by the prior art.

For completeness, it is noted that the dependent claims include additional features that are inventive over the art, e.g., the use of the mutant antibodies (having the desired combination of activities taught in the application) to block effector functions

of other allo- or auto-antibodies. However, such is not a ground for disunity under the applicable PCT rules (see Rule 13.4 PCT).

The applicants submit that the manner in which the Examiner has restricted the subject invention deprives Applicants of an opportunity to prosecute a generic claim (e.g., a claim of the entire scope of the broadest claims). Additionally, restriction of the case into 61 different inventions places an intolerable financial burden on Applicants. The filing fees alone approximate $45,000. A requirement that so profoundly disadvantages an applicant is clearly improper.

As basis for the restriction requirement, the Examiner has stated in Paper No. 12:

"Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention."

The "prior art" to which the Examiner refers in Paper No. 12 is Cole et al (J. Immunology 159:3613 (1997)). Applicants submit that the Examiner's reliance on Cole et al is not well founded.

As indicated on pages 6-7 of the subject application, the present invention provides a binding molecule that minimizes undesirable activities (for example, CDC) mediated by the IgG C domain — while retaining desirable activities mediated by the IgG C domain (for example, neonatal transport of IgG and inhibition of cellular responses). These latter activities are effected inter alia through the FcRn and FcIIb receptors. Thus the present invention provides an approach to altering the balance of binding to activatory versus inhibitory Fc receptors.

The invention is based on the use of chimeric antibody regions in which specific residues are altered, importantly, the amino acids incorporated are selected only from IgG parent molecules. The Examples provided in the subject application make it clear that chimeric antibodies of the invention, having residues that are not 'alien' to native IgG's, have combinations of activities not demonstrated or predicted by the parent antibodies, or the mutant antibodies of the art.

Cole et al differs from the present invention conceptually, functionally and structurally.

Conceptual Distinction

A detailed reading of Cole et al shows it is not concerned with natural effector functions of antibodies, for example, the triggering of cytotoxicity through Fc receptors on actual "effector" cells. In Cole et al, modification in the antibody are made to reduce the mitogenic effects on the target T-cells bearing the CD3 antigen to which the antibody is specific. These effects are attributed to the ability of the Fc receptors in Cole et al to bridge or to cross-link the CD3-bearing T cell bound by the antibody and a further Fc receptor-bearing cell, thereby eliciting a mitogenic signal that activates the T-cell - it is the further "accessory" cell that has the Fc receptor. In the first paragraph of the introduction of Cole et al (last sentence) the authors indicate that the role of Fc receptors in their system is analogous to immobolizing the antibody on a plastic surface. This clearly has nothing to do with Fc triggered effector functions of a cytotoxic antibody, as in the case of the present invention.

Functional Distinction

The Examiner states at page 11 of Paper No. 12 that the mutants of Cole et al bind FcRIIb. In fact, this is not the case.

The present specification describes the differences between FcIIb and FcIIa receptors (see pages 2-3, bridging; also pages 12-13). The claims of the subject application concern only the former.

The only data in Cole et al directly relating to FcRII is the FcRII-dependent T-cell retargeting assay using K562 cells. These express only FcRIIa of both HR (13IR) and LR (131H) allotypes (see page 3615 under "FcRII-dependent T-cell retargetting assay"). Further evidence that FcIIb is not expressed on these cells comes from the cited reference [23], Warmerdam et al (1991) J. Immunol 147: 1338) (copy of record). This reference shows that binding of human IgGI, 2 and 3 to these cells is almost completely inhibited by the monoclonal antibody IV.3 (see Figure 1 therein). As demonstrated in a later paper, this monoclonal does not bind well to FcIIb (Wannerdam et al (1993) Int. Immunol. 5:129-247, copy of record - see, e.g., page 241, second column, 7th line from bottom; page 244, first column, 8th line from bottom; page 244, second column, 7th line from bottom; also Figure 2).

The data in the retargeting assay indicate that the mutant tested does not bind to the K562 cells, that is, does not bind the FcII receptors that are present, contrary to the requirements of the present claim.

Summarizing, there is no reference to FcIIb in Cole et al, and it would be clear to the reader that the article concerns only the FcRIIa form of the FcRII receptors, which itself may not even be bound.

Structural Distinction

As regards the amino acid substitutions of Cole et al, they are not encompassed by the present claims.

It is acknowledged that Cole et al teaches certain antibody mutants (in their case, for the purpose of reducing the mitogenicity of anti-CD3 antibodies). Some of these mutants are modified in regions corresponding to one of those used in the present invention. However, Cole et al does not teach that the amino acids used should be specifically selected only from IgG parent molecules. As is very clearly shown in Table 1, page 3615 (referred to by the Examiner), most of the substitutions made in the 234-237 region are:

- Ala at position 234
- Glu at position 235
- Ala at position 237

None of these amino acids is taken from 'other' human IgGs (see first four rows of the table, which give the wild-type sequences). Indeed, generally speaking, Cole et al actually teaches away from the present invention in advocating the use of such 'non-natural' amino-acids for all of the mutants (Ml -M5), with which the paper was primarily concerned.

In one case (IgG4 mutant AA) there is a mutation:

Leu -> Ala at position 237

Applicants acknowledge that Ala is found in IgG2. Nevertheless, the presently claimed invention requires:

"...a chimeric effector domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulin are selected

from IgG1, IgG2 and IgG4 ... and wherein the chimeric domain is a human immunoglobulin heavy CH2 domain which has the following blocks of amino acids at the stated positions: 233P, 234V, 235A and 236G and 327G, 330S and 331S numbered with respect to the EU numbering system of Kabat, and is at least 98% identical to a CH2 sequence (residues 231-340) from human IgG1 or IgG4 having said modified amino acids."

As will be clear from the foregoing, IgG4 mutant AA of Cole et al has only a single amino acid found in a different immunoglobulin heavy chain CH2 domain.

Importantly, the IgG4 mutant AA was prepared purely for comparison with those which form the main teaching of Cole et al (i.e., M1-M5 in the Table) (see 5th line from end of page 3615). It is absolutely clear that the use of even a single residue from another IgG was pure coincidence. 'Ala' is apparently proposed because it is a small 'neutral' residue, not because it is found naturally in a different IgG subclass. Indeed, this approach to substitutions is no more than the prior art methodology of "ala scanning", as discussed, e.g., in Clark et al (1997) "IgG Effector Mechanisms" Chem. Immunol. 65:88-II0 - of record, see page 98, line 12). The strategy is used to detect and destroy functions, not to balance stimulatory and inhibitory functions, as is the case in the present invention.

Cole et al is acknowledged in the present application (page 5, lines 1-9) and was provided by the present assignee to the IPEA (it is D5b therein) to ensure that it formed part of the IPE procedure. In the IPER it is acknowledged that none of the cited documents (including D5b) teach the combination of the functional requirement of

FcRn\FcIIb binding with the particular (amino acid) changes within the specified immunoglobulin regions.

Conclusions

In conclusion, Cole et al is unrelated to the problem solved by the present invention. Further, Cole et al:

(i) does not demonstrate the combinations of functions required by the claims (e.g., FcIIb binding), and

(ii) does not teach the 2, 3 or 4 IgG-derived amino acid substitutions by which these functions are achieved, also as required by the claims.

Thus, Cole et al cannot be said to teach or suggest the present invention.

The Examiner has further made reference to Cole et al and Greenwood et al. in maintaining the restriction requirement in the Office Action of July 2, 2002 (Paper No. 17).

The above arguments with regard to the inapplicability of Cole et al are relevant to the Examiner's further remarks. Moreover, the re presented April 8, 2002 in response to the restriction requirement still apply.

In essence, the Examiner's further arguments in Paper No. 17 appear to be that since Cole et al and Greenwood et al allegedly disclose an effector region falling within the scope of the claim, all generic definitions in the claim were irrevocably disunified. Applicants submit that this is wrong in principle, since that would mean (to take a hypothetical situation) even if the USPTO were to accept a narrow genus (or even a single sequence) of effector molecules as being novel and unobvious per se, then Applicants would still need a different patent application for each variable region linked

to it, despite the fact that the former is the invention here - the latter is simply the way it can be applied by those skilled in the art. Unless an infinite number of cases were filed, the patent could always be avoided simply by anybody choosing to use it with a different variable binding site function. (The situation is analogous to someone inventing a new and unobvious engine for an automobile, and having to file a separate application for each different automobile in which it is used.)

Importantly, effector functions are, to all intents and purposes, independent of the variable binding site functions. This is illustrated in the attached table (Appendix III). The table shows the result obtained for each 'effector' mutation upon which the present claims are based (Δab, Δac, Δa) on various effector functions (given in the first column). In almost all cases, the tests were done using at least two different variable region specificities (selected from CAMPATH-1, Fog-1, B2 and 2D10, in the last column). In all cases where variable regions were compared, a common improvement in effector function, which correlates with the constant region, is apparent in the different specificities. The improvements in effector function are achieved irrespective of variable region specificity.

Thus, it is submitted that the arguments about the patentability or otherwise of the 'effector' invention should not affect the unity of the variable regions to which it is attached. Nevertheless, for completeness the following comments are offered regarding Cole et al. and Greenwood et al.

As regards Cole et al, extensive arguments are provided above. The Examiner disputes these stating at page 2 of Paper No. 17, that binding specificity is not a feature

of the claims, and also that Cole et al discloses an IgG2 wherein (see Paper No. 17, pg 2, 8th line from bottom):

"at least 2 amino acids at position 234 and 235 have been modified to V and A, respectively (See page 3615, Table 1, in particular). The said effector domain is capable of specifically binding to FcγIIb".

Respectfully, this statement is simply wrong. The original claim required that the amino acids be modified in the region in question. Modifications in the Cole et al table are underlined, and no single molecule has been modified to a V and an A. Cole et al's V234 and A235 are IgG2 native. Also, for completeness, the molecules of Cole et al have not been shown to bind FcRn and\or FcγRIIb.

As far as Applicants can discern, no novelty objection over Cole et al is pending. This indicates that the Examiner has accepted Applicants arguments and this repeated unity objection over Cole et al is seemingly included in error. That being the case, the finality of the requirement for restriction is improper and the Commissioner is urged to consider the following comments regarding Greenwood et al.

Greenwood et al is co-authored by one of the instant Applicants and is acknowledged in the application on page 8. It should be noted at the outset that this is based on a different technology, namely domain switching, and had different aims than those of the present invention.

Also, it is not a matter of record whether any or all of the Greenwood et al mutants are actually capable of binding FcRn and\or FcγIIb - which is a key feature of the current invention.

Moreover, Greenwood et al, fails to teach or suggest either 233P, 234V, 235A and 236 [G or no residue]. This clearly excludes all embodiments of Greenwood et al.

The claims are patentable over Greenwood for the reasons of record and the reference fails to establish a lack of unity of invention.

In the Office Action dated March 25, 2003 (Paper No. 22), the Examiner has repeated the restriction requirement, now apparently basing the restriction requirement on not only the above-noted references but also on Morgan et al and Chappel et al..

These further references, alone or in combination, fail to establish a lack of unity of invention of the presently claimed invention. The Examiner has not rejected the claims for lack of novelty over any one of these references. The Examiner therefore acknowledges that the claimed invention is novel over each of the cited references. As the claimed invention is submitted to be patentable over the combination of cited art, for the reasons detailed below, the claims are submitted to share a special technical feature, and all of the claimed subject matter should be examined in this one application. The restriction requirement should be withdrawn.

Greenwood et al is concerned only with the effector functions ADCC and complement lysis. Thus even the 'closest' mutants prepared (DS111/41 and DS1141) differ in the identity of the 233-236 residues which are required by the claims and also include several changes that are irrelevant to the present invention (274, 296, 300, 309 and 339) (see Appendix III).

Interestingly, a comparison between Fig 3 of Greenwood et al and the present application (Fig 9 and 10a for CAMPATH and Fog-1 respectively) suggests that even in respect of ADCC, the mutants of the citation are inferior to some of the preferred

mutants of the present invention (e.g., none of the Greenwood et al mutants improve over IgG4).

By comparing:

G1Δb, G1Δc, G1Δab, and G1Δac, with

G1Δa or D2's DS111/41 and DS1141

it seems that the 233-236 residues are an important factor in ADCC, which is not taught or suggested by Greenwood et al.

More importantly, however, Greenwood et al is entirely silent in respect of the other effector functions required by the claims, i.e., does not even teach (i) the desirability of balancing these other functions (FcRn and\or FcγRIIb), (ii) the mutations which would achieve the desired functions, or (iii) whether making "extra" mutations would negate or affect the ADCC and lysis functions. The present invention addresses all of these points.

Examiner states (Paper No. 17, page 16) that:

"Greenwood et al teach that it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy...."

but this is scarcely a teaching or even an indication of how all such antibodies can be prepared, and Applicants submit it is simply untenable to assert that this statement would have rendered all such improved antibodies "obvious".

Morgan et al is concerned with C1q, FcγRI, and FcγRIII binding. As with Greenwood et al above, this citation is not primarily concerned with other effector

functions required by the claims (e.g., minimizing ADCC - indeed see the relatively poor results given in Figure 4 for the mutants taught)

Certainly it does not teach (i) the desirability of balancing these and other functions (FcRn and\or FcγRIIb), (ii) the mutations which would achieve the desired functions, or (iii) whether making "extra" mutations would negate or affect the other functions elsewhere in the molecule. Thus there is nothing which would lead one of ordinary skill in the art to combine Morgan et al with Greenwood et al, and even if such a combination had been made, this teaching would not have resulted.

Regarding the comment on page 18 line 13 "....still capable of binding to FcRn such as FcgRI", Applicants do not understand this remark and clarification is requested. As the Commissioner is no doubt aware, these receptors and effector functions are quite distinct (see pages 2-3 of the present application).

Chappel et al is, as the title suggests, an attempt to identify the FcγRI binding site using IgG1 and IgG2 sequences. The authors correctly focussed attention on the lower hinge region sequences. However, unlike the present invention, Chappel et al was concerned only with the high affinity receptor FcgRI, and not the low affinity receptors. Additionally, unlike the present invention, the citation used primarily single point mutation, or swapping the entire CH2 domain (10 changes), rather than the combinations of point mutations taken from other wild-type IgG sequences.

As regards Cole et al, extensive remarks are provided above and have been made of record, and this citation is also discussed above in relation to unity, all such comments being incorporated here by reference.

In conclusion, individually, each residue specified in the claims may appear in the literature (indeed, since they are all wild-type residues from different IgGs, it is inevitable they will appear, individually, or in sub-groups, in thousands of publications). Likewise there is a literature on each of the effector functions, since Applicants did not invent those individual functions, or even discover them. However, nobody had previously thought to combine those functions using the precise combinations of mutations specified in the present claims, and none of the documents cited by the Examiner would have lead the ordinarily skilled person to do that. The Examiner's assertion on page 20 of Paper No. 17, final paragraph, that combining the cited art would give one of ordinary skill in the art a reasonable expectation of producing [prior claim 8] is just that - an assertion. A combination of these 4 documents could give virtually anything (or everything) in terms of mutated CH2 regions but that would not have made all mutant CH2 regions obvious. The claims therefore are submitted to share a special technical feature and the restriction requirement should be withdrawn.

In response to remarks similar to those presented above, the Examiner has responded in Paper No. 22, that, in effect, the recitation of "has" opens the claims to inclusion of Greenwood's additional amino acids. With due respect to the Examiner, whether the claims are open in their transition phrase does not establish that it would have been obvious from the Examiner's combination of cited art to make a combination of mutations discovered and claimed by the applicants. Moreover, the Examiner's dismissal of the applicants' previous arguments based on the interpretation of the previously claimed recitation of "FcRn and/or FcγRIIb" is moot in view of the pending claims. See, Amendment submitted separately herewith. The Examiner has further

dismissed the applicants' comments regarding Greenwood noting that a product is not limited by the process by which it is made. While this may be true in interpretting product claims for purposes of patentability, the Commissioner is urged to appreciate that the purpose and/or motivation of Greenwood is fundamental to the consideration of whether one of ordinary skill in the art would have been motivated by Greenwood, or any of the cited art, to make the presently claimed invention, with a reasonable expectation of success. For all the reasons of record, the applicants submit such an ordinarily skilled worker would not have been so motivated.

A further more detailed analysis of the cited art is provided in the Remarks of the attached Amendment which, for economy, is incorporated herein by reference. A separate copy of the Amendment is attached, and marked COPY on page 1 of the same, for purposes of consideration of these Remarks with the present PETITION. The Commissioner is requested to contact the undersigned in the event anything further is required in this regard.

Other issues — improper grouping of claims

It will be clear from the foregoing that the requirement for restriction is based on a misinterpretation of Cole et al., as well as the other cited art However, for completeness, for following points are also made:

i) Group I + others: Campath — this binds CD52 (Fog binds RhD)

ii) Group X: Lutheran is not a hormone but a red cell antigen

iii) Groups XLVI and LIX: platelet GPVI has nothing to do with haemolytic disease but is concerned with coronary artery disease (cf. Groups XLVII and LX).

Favorable consideration and a Decision on the present Petition, prior to a further Action by the Examiner, are requested.

No fee is believe to be required for consideration of the present Petition as the same is only required due to Patent Office error in the Examiner maintaining the restriction requirement. The Commissioner is authorized however by the attached cover sheet to charge the undersigned's Deposit Account 14-1140 for any fee required for consideration of the present Petition.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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iii) Appendix III - Table of unity

Effects of Δab and Δac mutations on IgG1 activity and of Δa mutation on IgG2 activity in various test systems. The variable regions contexts in which the constant regions were tested are listed. They are CAMPATH-1 (CD52 specificity), Fog-1 (anti-RhD), B2 (anti-human platelet antigen-1a) and 2D10 (anti-vascular adhesion protein-1). The reductions in activity given represent the approximate increase in antibody concentration necessary to achieve the same level of activity as IgG1 or IgG2.

IgG1Δab = 233P, 234V, 235A and 236- and 327G, 330S and 331S present in the tested molecule.
IgG1Δac = 233P, 234V, 235A and 236G and 327G, 330S and 331S present in the tested molecule.
IgG2Δa = 233P, 234V, 235A and 236- and 327G, 330S and 331S present in the tested molecule.

(see patent application Figure 15)

Function	Effect on Δab mutation on IgG1 activity	Variable regions with which tested
Binding to:		
FcγRI	10^4-fold reduction to background	CAMPATH-1, Fog-1, B2
FcγRIIa 131R	8-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIa 131H	16-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIb1*	4-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIIb NA1	>100-fold reduction to background	Fog-1, B2
FcγRIIIb NA2	>100-fold reduction to background	Fog-1, B2
Monocyte activation	100-fold reduction	Fog-1, B2
Complement lysis	>50-fold reduction to background	CAMPATH-1
ADCC	>100-fold reduction to background	CAMPATH-1, Fog-1

Function	Effect on Δac mutation on IgG1 activity	Variable regions with which tested
Binding to:		
FcγRI	10^4-fold reduction to background	CAMPATH-1, Fog-1, B2
FcγRIIa 131R	10-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIa 131H	32-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIb1*	4-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIIb NA1	>100-fold reduction to background	Fog-1, B2
FcγRIIIb NA2	>100-fold reduction to background	Fog-1, B2
Monocyte activation	100-fold reduction	Fog-1, B2
Complement lysis	>50-fold reduction to background	CAMPATH-1

ADCC	>100-fold reduction to background	CAMPATH-1, Fog-1

Function	Effect on Δa mutation on IgG2 activity	Variable regions with which tested
Binding to:		
FcγRI	remained at background	CAMPATH-1, Fog-1, 2D10
FcγRIIa 131R	no effect	CAMPATH-1, Fog-1, 2D10
FcγRIIa 131H	8-fold reduction	CAMPATH-1, Fog-1, 2D10
FcγRIIb1*	no effect	CAMPATH-1, Fog-1, 2D10
FcγRIIIb NA1	remained at background	Fog-1, 2D10
FcγRIIIb NA2	remained at background	Fog-1, 2D10
Monocyte activation	remained at background	Fog-1
Complement lysis	>20-fold reduction to background	CAMPATH-1, 2D10
ADCC	100-fold reduction	CAMPATH-1, Fog-1

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Examiner: Huynh, P.

For: BINDING MOLECULES DERIVED FROM IMMUNOGLOBULINS WHICH DO NOT TRIGGER COMPLEMENT MEDIATED LYSIS

* * * * * * * * * * * *

January 26, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

Responsive to the Official Action dated March 25, 2003, entry and consideration of the following amendments along with the attached RCE, are requested; the period for response having been extended up to and including January 26, 2004, by submission of the Notice of Appeal and Notice of Appeal fee and three month extension petition and three month extension petition fee on September 25, 2003, and submission of the attached RCE with a two month extension petition and two month extension fee, attached. Return of an initialed copy of the attached PTO 114 Form, pursuant to MPEP § 609, is also requested.

A personal interview with the Examiner and the Examiner's Supervisor is hereby requested prior to the mailing of the Examiner's next Action in the event

the application is considered to not be in condition for allowanc or the restriction requirement is not withdrawn in response to the pres nt Am ndment and attached Rule 181 Petition. The Examiner is requested to contact the undersigned to arrange a time for the interview convenient to the schedules of the Examiner and the Examiner's Supervisor. A separate Request for an interview is attached.

IN THE ABSTRACT:

Please insert the attached new ABSTRACT in place of the Abstract filed January 2, 2002

IN THE SPECIFICATION:

Amend the specification as follows:

Please replace the paragraph beginning at page 33, line 19, as amended in the Response dated May 18, 2001, with the following rewritten paragraph:

Figure 17

This shows the Sequences of certain modified and wild-type CH2 sequences (G1 (SEQ ID NO:4), G2 (SEQ ID NO:5), G3 (SEQ ID NO:6), G4 (SEQ ID NO:7), G4Δb (SEQ ID NO:11), G4Δc (SEQ ID NO:12), DS111/41 (D2) (SEQ ID NO:8), HuG2/G4 (D10) (SEQ ID NO:11), ~~SEQ ID NO:4-SEQ ID NO:12), including those designated~~ G1Δab (SEQ ID NO:1), G2Δa (SEQ ID NO:2), and G1Δac (SEQ ID NO:3)).

IN THE CLAIMS:

Amend the claims as follows:

Claims 1-15 (Cancelled).

16. (Currently Amended) An isolated nucleic acid comprising a nucleotide sequence encoding the effector domain of the binding molecule as claimed in claim 32~~claim 1~~.

17. (Currently Amended) An isolated nucleic acid comprising ~~as claimed in claim 16 wherein the~~ a nucleotide sequence ~~encodes~~ encoding a binding molecule as claimed in claim 32~~claim 1~~.

18. (Withdrawn) A nucleic acid as claimed in claim 16 which is a replicable vector.

19. (Withdrawn) A nucleic acid as claimed in claim 18 wherein the nucleotide sequence is operably linked to a promoter.

20. (Withdrawn) A host cell comprising or transformed with the vector of claim 19.

21. (Currently Amended) A process for producing a binding molecule as claimed in claim 32~~claim 1~~, the process comprising the step of modifying a nucleotide sequence

encoding a first human immunoglobulin heavy chain C_H2 such that 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain corresponds to an amino acid from a second human immunoglobulin heavy chain C_H2 domain,

wherein the region is selected from the 2 discrete regions numbered residues 233-236, and 327-331 in accordance with the EU numbering system,

and wherein in each case the human immunoglobulin is selected from IgG1, IgG2 and IgG4.

22. (Withdrawn) A process as claimed in claim 21 wherein 2 amino acids in 1 region of the C_H2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy chain C_H2 domain.

23. (Currently Amended) A method of binding a target molecule comprising contacting said target molecule with ~~Use of~~ a binding molecule ~~or nucleic acid as claimed in claim 1~~of claim 32 under conditions allowing binding ~~to bind a target molecule with said binding molecule~~.

24. (Currently Amended) A method of ~~Use as claimed in~~ claim 23 wherein the target molecule is FcγRIIb, which binding causes inhibition of one or more of: B cell activation; mast cell degranulation; phagocytosis.

25. (Currently Amended) A method of ~~Use as claimed in~~ claim 24 to prevent, inhibit, or otherwise interfere with the binding of a second binding molecule to the target molecule.

26. (Currently Amended) A method of ~~Use as claimed in~~ claim 25 wherein the second binding molecule is an antibody.

27. (Currently Amended) A method of ~~Use as claimed in~~ claim 25 wherein the target molecule is selected from: the RhD antigen of red blood cells; an HPA alloantigen of platelets; a neutrophil antigen; a T-cell receptor; integrin; GBM collagen; Der P1; HPA-1a; VAP-1; laminin; lutheran; platelet glycoprotein VI; platelet glycoprotein Ia/IIa.

28. (Currently Amended) A method of ~~Use as claimed in~~ claim 24 for the treatment of a patient for a disorder selected from: Graft-vs-host disease; host-vs-graft disease; organ transplant rejection; bone-marrow transplant rejection; autoimmunity such as vasculitis, autoimmune haemolytic anaemia, autoimmune thrombocytopenia and arthritis; alloimmunity such as foetal/neonatal alloimmune thrombocytopenia; asthma and allergy; chronic or acute inflammatory diseases such as Chrohn's; HDN; Goodpastures, sickle cell anaemia, coronary artery occlusion.

29. (Currently Amended) A method of ~~Use as claimed~~ claim 23 wherein the binding molecule is administered to a patient, or optionally in cases where the patient is an unborn infant, to the mother of the patient.

Claim 30 (Canceled).

31. (Withdrawn) An oligonucleotide selected from:

MO22BACK: 5' TCT CCA ACA AAG GCC TCC CGT CCT CCA TCG AGA AAA 3'

MO22: 5' TTT TCT CGA TGG AGG ACG GGA GGC CTT TGT TGG AGA 3'

MO7BACK: 5' TCC TCA GCA CCT CCA GTC GCG GGG GGA CCG TCA GTC 3'

MO21: 5' GAC TGA CGG TCC CGC GAC TGG AGG TGC TGA GGA 3'

32. (Currently Amended) A binding molecule which is a recombinant polypeptide comprising:

(i) a binding domain capable of binding a target molecule, which binding domain is the binding site of an antibody, and

(ii) an effector domain having an amino acid sequence ~~substantially~~ homologous to all or part of a constant domain of a human immunoglobulin heavy chain;

wherein the binding molecule is capable of binding the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, and capable of specifically binding ~~FcRn and\or FcγRIIb~~ FcγRIIb and optionally FcRn,

and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4,

and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa and FcγRIII and a reduced ability to mediate complement lysis by comparison with said human immunoglobulin heavy chain C_H2 domains

and wherein the chimeric domain is a human immunoglobulin heavy chain CH2 domain which has the following blocks of amino acids at the stated positions: 233P, 234V, 235A and 236G and 327G, 330S and 331S numbered with respect to the EU numbering system of Kabat, and is at least 98% identical to a C_H2 sequence (residues 231-340) from human IgG1 or IgG4 having said modified amino acids.

33. (Currently Amended) The binding molecule as claimed in claim 32 wherein the effector domain is selected from G1Δac (SEQ ID NO:3) or G4Δc (SEQ ID NO:12) as shown in Figure 17.

Claim 34. (Cancelled)

35. (Previously Presented) The binding molecule as claimed in claim 32 wherein the effector domain is derived from a first human immunoglobulin heavy chain CH2 domain wherein at least 1 amino acid in at least 1 region of the CH2 domain has been modified to the corresponding amino acid from a second, different, human immunoglobulin heavy chain CH2 domain, and

wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with the first or second human immunoglobulin heavy chain CH2 domain.

Claim 36. (Cancelled)

37. (Previously Presented) The binding molecule as claimed in claim 32 wherein the binding domain derives from a different source to the effector domain.

38. (Previously Presented) The binding molecule as claimed in claim 32 wherein the binding domain is capable of binding any of: the RhD antigen of red blood cells; an HPA alloantigen of platelets; a neutrophil antigen; a T-cell receptor; integrin; GBM collagen; Der P1; HPA-1a; VAP-1; laminin; lutheran; platelet glycoprotein VI; platelet glyprotein Ia/IIa.

39. (Currently Amended) ~~A binding~~ The binding molecule as claimed in claim 38 wherein the binding domain is selected from that of anti-CD52 antigen found on human lymphocytes; FOG1; OKT3; B2 (anti-HPA-1a); VAP-1; murine anti-α3 (IV) NC1; YTH12.5 (CD3); 2C7 (anti-Der p1); anti-laminin; or anti-lutheran.

40. (Previously Presented) A pharmaceutical preparation comprising a binding molecule as claimed in claim 32 plus a pharmaceutically acceptable carrier.

41. (Currently Amended) A binding molecule which is a recombinant polypeptide comprising:

(i) a binding domain capable of binding a target molecule, which binding domain is the binding site of an antibody, and

(ii) an effector domain having an amino acid sequence ~~substantially~~ homologous to all or part of a constant domain of a human immunoglobulin heavy chain;

wherein the binding molecule is capable of binding the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, and capable of specifically binding ~~FcRn and\or FcγRIIb~~ FcγRIIb and optionally FcRn,

and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4,

and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa and FcγRIII and a reduced ability to mediate complement lysis by comparison with said human immunoglobulin heavy chain C_H2 domains

and wherein the chimeric domain is a human immunoglobulin heavy chain CH2 domain which has the following blocks of amino acids at the stated positions: 233P, 234V, 235A and no residue at 236; and 327G, 330S and 331S, numbered with respect to the EU system of Kabat and is at least 98% identical to a CH2 sequence (residues 231-340) from human IgG1 or IgG2 having said modified amino acids.

42. (Previously Presented) The binding molecule as claimed in claim 41 wherein the effector domain is selected from G1Δab or G2Δa.

Claim 43. (Cancelled)

44. (Previously Presented) The binding molecule as claimed in claim 41 wherein the effector domain is derived from a first human immunoglobulin heavy chain CH2 domain wherein at least 1 amino acid in at least 1 region of the CH2 domain has been modified to the corresponding amino acid from a second, different, human immunoglobulin heavy chain CH2 domain, and

wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with the first or second human immunoglobulin heavy chain CH2 domain.

Claim 45. (Cancelled)

46. (Previously Presented) The binding molecule as claimed in claim 41 wherein the binding domain derives from a different source to the effector domain.

47. (Previously Presented) The binding molecule as claimed in claim 41 wherein the binding domain is capable of binding any of: the RhD antigen of red blood cells; an HPA alloantigen of platelets; a neutrophil antigen; a T-cell receptor; integrin;

GBM collagen; Der P1; HPA-1a; VAP-1; laminin; lutheran; platelet glycoprotein VI; platelet glyprotein Ia/IIa.

48. (Currently Amended) The binding molecule as claimed in claim 47 ~~claim 38~~ wherein the binding domain is selected from that of anti-CD52 antigen found on human lymphocytes; FOG1; OKT3; B2 (anti-HPA-1a); VAP-1; murine anti-α3 (IV) NC1; YTH12.5 (CD3); 2C7 (anti-Der p I); anti-laminin; anti-lutheran.

49. (Previously Presented) A pharmaceutical preparation comprising a binding molecule as claimed in claim 41 plus a pharmaceutically acceptable carrier.

REMARKS

Reconsideration is requested.

A new Abstract is provided of the appropriate length, as required by the Examiner. Withdrawal of the objection to the disclosure based on the same is requested.

The specification has been amended to include a more detailed listing of the sequences of Figure 17. Claim 33 has been similarly amended.

Claims 1-15, 30, 34, 36, 43 and 45 have been canceled, without prejudice.

Claims 16-29 and 31 have been withdrawn from consideration by the Examiner.

Claims 32 and 41 have been further amended above, consistent with the specification. No new matter has been added.

Claims 16-29, 31-33, 35, 37-42, 44 and 46-49 are pending.

Attached is a Request for Continued Examination (RCE). Withdrawal of the finality of the Office Action of March 25, 2003 (Paper No. 22) is requested along with a new non-final Office Action on the merits of the claimed invention.

Consideration of the attached Information Disclosure Statement, along with the information cited therein, and return of an initialed copy of the attached PTO 1449 Form, pursuant to MPEP § 609, are requested.

Consideration of the attached Rule 181 Petition, requesting that the Commissioner invoke his supervisory authority and withdraw the restriction requirement of December 6, 2001 (Paper No. 12), and a favorable Decision on he same, prior to the Examiner's next Action on the merits, are requested.

A personal interview with the Examiner and the Examiner's Supervisor is hereby requested prior to the mailing of the Examiner's next Action in the event the application is considered to not be in condition for allowance or the restriction requirement is not withdrawn. The Examiner is requested to contact the undersigned to arrange a time for the interview convenient to the schedules of the Examiner and the Examiner's Supervisor. A separate Request for an interview is attached.

The Section 112, first paragraph, "enablement" and "written description" rejections of claims 32-49 are traversed. Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing remarks.

While the Examiner's apparent thoroughness in reciting the language of every claim on pages 4 to 7 and on page 9 onwards, of Paper No. 22, the applicants understand the Examiner's concern to be as follows (the Examiner is requested to advise the undersigned in the event the Examiner's position has been mischaracterized and/or misunderstood, so that the applicants may fully understand any and all outstanding rejection(s)):

a) Alleged non-enablement of any binding domain (e.g. capable of binding any target molecule, or treating any disease) over those acknowledged by the Examiner as being enabled on page 4 of Paper No. 22 (RhD, CAMPATH-1).

b) Alleged non-enablement of an effector domain having further amino acid changes over those acknowledged by the Examiner as being enabled on page 4 of Paper No. 22 (effectively those recited in the preferred embodiments, and possibly 98% identical thereto).

c) Alleged non-enablement of pharmaceutical preparations.

Consideration of the following comments and remarks in response are requested with withdrawal of the rejection.

The alleged evidence and reasoning proposed by the Examiner is submitted, with due respect, to be speculative and general, and is believed to not acknowledge the actual claimed subject matter or the teaching of the application, and/or data provided in applicants' previous response.

The Examiner's objections, in effect, are submitted to amount to a criticism that the claims are broader than the preferred individual sequences of the examples. However the applicants submit that the Examiner's attempt to allow only a preferred embodiment is inappropriate, especially where, as here, the specification teaches one of ordinary skill how to make and use the presently claimed invention, and that one of ordinary skill in the art would appreciate from the disclosure that the applicants were in possession of the claimed invention at the time the application was filed.

The applicants submit, for example, whether, in terms proffered by the Examiner, in the light of all of the *Wands* factors, the scope of enablement bears a "reasonable correlation" to the scope of the claims" (*see* e.g. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)) which test is clearly met.

Consideration of the above-noted summary of the Examiner's objections are provided in the following in more detail:

a) Binding domains

Firstly, the applicants note, for completeness, that the Examiner is factually incorrect in a number of assertions. Thus (page 8, line 12) in fact the specification "discloses" several binding domains e.g. page 15, line 1 – page 24, line 17 – see also

Example 7. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The burden placed on the Examiner is reflected in the MPEP Section 706.03. The Examiner has, with due respect, not met this burden.

Secondly, the Examiner appears to be misconstruing the claims (page 9, line 5). If the applicants were indeed explicitly claiming that **each** claimed binding molecule was able to treat "**any** disease" (emphasis added) then that might be grounds of objection, but there is nothing in the claims or the specification to support such an interpretation. Briefly, the invention has utility for inhibiting undesirable binding interactions (for example antibody-antigen, or other protein-protein, interactions) where these occur (see page 13, lines 17-28). Several examples of such interactions, diseases, and binding domains are given in the specification. On the basis of such utility it is perfectly normal to claim products *per se*, as in the presently elected claims. Therefore it is not clear to the applicants where the Examiner's objections in respect of "**any** disease" arise from. Clarification is requested in the event this basis of rejection is maintained.

Thirdly, referring to page 9, line 4, of Paper No. 22, the Examiner has not provided any evidence or technical reasoning substantiating the fact that binding molecules including antibody binding sites cannot be **made** or **used**. The modified effector regions were (of necessity) demonstrated using two different particular, prior art, binding domains since this was the only way of demonstrating the effector activities, but there is absolutely no evidence or technical reasoning to support the idea that the inhibitory activities could not be achieved using other targets and binding domains, for

the treatment of wide variety of indications resulting from undesirable binding interactions (see also B2 and 2D10 results in Appendix III of the previously filed response – see also above).

It is well established that constant regions can be mixed and matched with variable binding domains (see e.g. Clark, 1997 of record – pg 88, 9th line from bottom – "[immunoglobulins exist as]...C region domains associated with virtually any of the possible V regions"). It is therefore entirely conventional in this area of technology that inventions made in respect of constant regions should be claimed without reference to variable regions and vice versa. *See*, for example the claims of the Genentech cases cited in the attached Information Disclosure Statement (i.e., WO 99/51642 and U.S. Patent No. 6,194,551). While the applicants appreciate that every patent application is treated separately based on the facts of the case, applicants should be able to expect the Commissioner, acting through the examining corps, to provide a consistent approach to a given issue, absent well founded reasons to the contrary.

Therefore the objection should be withdrawn.

b) Effector domains

The Examiner (page 9, line 7, of Paper No. 22) is understood to object to the term "has" as being open ended. This is understood by the applicants to give rise to the Examiner's grounds of rejection because, essentially, it is asserted that certain amino acid changes may allegedly impair the function of the C_H2 domain with respect to the effector functions required by the claims.

However the "evidence" cited does not support the Examiner's position.

Specifically, the section of the specification cited by the examiner on page 9, lines 20-25, very clearly refers to the modifications made in the present application at positions 233-236 & 327, 330-1 with respect to the wild-type. The submit that while the effects obtained by the totality of these changes was unpredictable, the identities of the amino acids of these positions are now sacrosanct. Therefore the sensitivity of activities to changes at these positions is irrelevant.

Moreover, the disclosure of Morgan et al. cited by the Examiner on page 9, lines 26-28 likewise refers to position 235 which is 'fixed' in the claims. Of course one could equally point to, say, Morgan's K320A which does not appear to affect the activities of IgG1 (see Table 2) and deduce that changes outside of 233-236 & 327, 330-1 do not affect properties.

The Examiners assertions from page 9, line 30 – page 10, line 4, are therefore simply unsubstantiated allegations. To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must, at a minimum, provide some evidence or technical reasoning substantiating those doubts. *See*, MPEP § 2164.04.

Nevertheless, purely for procedural expediency claim 32 now has included a "98% limitation" as per claim 41 - with respect to the Examiners assertions from page 10, line 26, the applicants note that on page 4 through to page 5, line 29, the Examiner acknowledges that the specification is "...enabling for...CH2 domain...at least 98 & [sic, %] identical to a CH2 sequence (residues 231-240) [sic, 231-340] from human IgG1 or IgG2 having said modified amino acids...".

In respect of Ngo et al., the applicants note, for completeness, that the applicants are not attempting to define structure purely by reference to activities (cf. TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT - CHEMICAL/BIOTECHNICAL APPLICATIONS, Example N: DNA). In any case, by contrast with Ngo et al., the crystal structure of IgG is known (e.g. Clark, 1997 of record – page 92 and legend page 93), and there is a considerable literature on the subject. Certainly, in the light of this and the present disclosure it would be possible for the ordinarily skilled person to predict residues which are non-sacrosanct in the claims, and which would not be expected to destroy activities, e.g. because they were not near the sacrosanct residues, or because they were conservative substitutions.

The reference to Kuby et al., appears to the applicants to be irrelevant since it does not seem to be concerned with engineering immunoglobulins.

Bearing in mind the above, a consideration of the *Wands* factors makes it clear that the presently claimed subject matter is supported by an enabling disclosure. Taking each "factor" in turn, the applicants submit the following:

(1) The breadth of the claims: all claims are based on natural CH2 regions in which mutations have been introduced such as to give specific amino acids at positions 233-236 & 327, 330-1. Such molecules have been compared with other mutations at those positions and wild type immunoglobulins and the particular mutations have been shown to result in a desirable combination of activities (which result was not obvious from the prior art – see comments below). The claims define CH2 regions in which these precise amino acids have been introduced.

(2) The nature of the invention: the invention is in the field of engineering immunoglobulins. The art and level of skill in this art was advanced at the time of the present invention.

(3) The state of the prior art: there is a considerable literature in the field of engineering immunoglobulins, albeit that none of the art taught or suggested the precise combination of residues of the present claims. Since the specification need not disclose what is well-known to those of ordinary skill in the art, and preferably omits that which is well-known to those of ordinary skill and already available to the public (*In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)) an entire history and manual for immunoglobulin engineering, and CH2 effector function, is not disclosed, although a discussion of the latter is given in Clark et al. (1997) of record.

(4) The level of one of ordinary skill: in terms of the ability to prepare and test mutants for different activities this is high – as evidenced by many of the publications of record, including those relied upon in the final rejection (albeit that none of these suggested the presently claimed mutants). It is thus clear that in the light of the present disclosure, immunoglobulins comprising the precisely defined mutations of the claimed invention could be prepared without undue burden, and if required further mutations could be introduced (e.g. to match known allotypes). Similarly such constant regions could be combined with different binding domains by those skilled in the art without undue burden.

(5) Amount of Direction or Guidance Present: Sufficiency of Disclosure/Predictability/ Non-Predictability: As a generality, the applicants accept that changes to primary structure can affect higher order structure and activity in ways which

are not always certain. The Examiner has repeatedly referred to unpredictability in the art. However, as stated in the TRAINING MATERIALS (cited supra):

"It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. Wands, Id. at 737 & 740, 8 USPQ2d at 1404 & 1407."

In the present case mutations in the 233-236 & 327, 330-1 region were prepared in 8 different combinations, which were compared with each other and 3 different wild-type immunoglobulins in many different experiments (see e.g. Figures 1 to 14) including more than one variable region for increased confidence. The consistent results were that immunoglobulins including the claimed combinations of residues gave the required properties in both IgG1, 2 and 4 backgrounds and irrespective of which binding domain was used. Since the claimed subject is based on said mutations in said backgrounds, it will be clear to one of ordinary skill in the art that sufficient direction is provided to practice the presently claimed invention.

Additionally the applicants submit that it would be inequitable to insist upon recitation in the claims of only the precisely recited sequences. As stated in *In re Goffe*, 191 USPQ 429 (CCPA 1976):

"For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must

adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts" (Emphasis supplied).

For all of the above reasons, the applicants believe the Section 112, first paragraph, rejections should be withdrawn.

c) Pharmaceutical preparations\in vivo examples

General

At the outset, and referring to Riechmann et al. page 323, abstract and 1st paragraph, it is clear that immunoglobulins (both naturally occurring in serum, and engineered) had been used as therapeutics for over 100 years prior to the date of the present application. A list of "modified" therapeutic antibodies undergoing clinical trials in humans can be found at: http://www.path.cam.ac.uk/~mrc7/humanisation/antibodies.html. There can be no question therefore that immunoglobulins have been, and can be, used as therapeutics.

In vitro – in vivo

The presently claimed molecules have been tested for numerous effector functions as described in Figures 1 to 14 and Examples 1 to 6b. Moreover, they have been shown to inhibit the response of monocytes to immunoglobulins sensitised cells and inhibit the killing of targeted cells through complement lysis or ADCC. As discussed in the Examples e.g. page 49, lines 30-34, the tests used have been those already shown to be useful in predicting *in vivo* pathology. The tests on page 50 studied CL responses which were indicative of haemolytic disease in the newborn.

Therefore *prima facie* both generally and specifically it is reasonable to assume that the presently claimed immunoglobulins could be reasonably be used *in vivo* by one of ordinary skill in the art. The 3 "reasons" given on page 12, lines 5-9 of Paper No. 22, are submitted to be entirely speculative and completely unsupported by any evidence of record, and in particular the widely recognized and well established use of antibodies for therapy.

The Examiner's objections are again believed to be simply that the claims are broader than the examples. Such is not a sufficient ground to sustain a rejection under Section 112. The presence of working *in vivo* examples are not required by the statute, rules, or the case law. Indeed as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985), all that is required is that:

"...based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." (in terms of extrapolation to other binding domains – see (a) above.)

With further regard to the Examiner's "written description" rejection, the above comments equally well apply in response to the Examiner's remarks which appear to be similar in their basis to the Examiner's remarks relating to the "enablement" rejection. Moreover, the Examiner is requested to note that the specification does describe several binding domains e.g. page 15, line 1 – page 24, line 17 – see also Example 7. The examiner has not commented at all on the applicants reference in their previous

response to Example 16 of the "Synopsis of application...". Clarification is requested in the event the Section 112 rejections of the claims are maintained.

Withdrawal of the Section 112, first paragraph, rejections of the claims is requested.

Claim 39 has been amended above to obviate the objection to the same found in ¶ 11. of Paper No. 22. Withdrawal of the objection is requested.

Claim 48 has been amended above to obviate the Rule 75 objection of the same stated in ¶ 12. of Paper No. 22. Withdrawal of the Rule 75 objection of claim 48 is requested.

To the extent not obviated by the above amendments, the Section 112, second paragraph, rejection of claims 32, 34, 41 and 43, is traversed. Reconsideration and withdrawal of the rejection are requested as claims 32 and 41 have been amended to delete the reference to "substantially", without prejudice, to advance prosecution. Moreover, claims 34 and 43 have been canceled, without prejudice, to advance prosecution. The Examiner's reference to the previously "pointed out" passage in ¶ 14. of Paper No. 22, is not understood as the applicants previously responded by referring to pare 14, lines 29-30 of the specification (*see*, page 14 of the Remarks of the Amendment dated January 2, 2002), which is a reference to WO 92/16562, relating to "null-allotypic". Clarification is requested in the event any rejection based on the same is maintained. Withdrawal of the Section 112, second paragraph, rejection is requested

The Section 103 rejection of claims 32-37, 39-46 and 49 over Greenwood et al in view of Morgan et al, Chappel et al and Cole et al. is traversed. The Section 103 rejection of claims 34 and 43 over the above-noted combination of art, taken further in

view of WO 95/05468, is traversed. Finally, the Section 103 rejection of claims 38, 39, 47 and 48 over Greenwood et al, Morgan et al, Chappel et al and Cole et al, taken further in view of USP 5,831,063 is traversed. Reconsideration and withdrawal of the Section 103 rejections are requested in view of he following distinguishing comments.

The Examiner's analysis is, with due respect, based on an inappropriate hindsight analysis of the claimed invention. The Examiner is urged to appreciate that motivation to combine the art and to make the claimed invention must come from the cited art, as opposed to the applicants' specification.

Only by selectively reading and artificially combining sections of the cited art documents has the Examiner arrived at some of the features of the claims, and has overlooked or ignored other claimed features, e.g. in terms of required functionality.

At the outset, the Examiner is submitted to have overlooked or ignored the fact that the cited art was not concerned with the problem addressed by the presently claimed invention, namely to provide CH2 domains:

having lowered complement and other activatory activities (indeed, lower than the progenitor wild-type immunoglobulins in some respects) while,

minimising immunogenicity, and

retaining (at least) FcγRIIb binding.

The Examiner's analysis has overlooked or ignored these properties. In respect of the first property the examiner is reminded that, as stated by the CAFC (*In re Wright*, 6 USPQ2d 1959, 1961 (CAFC 1988) (emphasis added)

"The determination of whether a novel structure is or is not 'obvious' requires cognizance of the properties of that structure and the problem which it solves, viewed in light of the teachings of the prior art."

and in respect of the remaining two properties:

"the question is whether what the inventor did, would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working." (Emphasis added.) *In re Wright*, 6 USPQ 1959, 1961 (Fed. Cir. 1989).

In the present case, the "problem upon which the inventor was working" was not even that being considered in the cited documents. However this point has not been taken into account by the Examiner, who has focused purely on mere structural substitutions and differences, rather than focusing on the invention as a whole, as required by the Law and the Courts.

The Examiner is urged to appreciate that obviousness under 35 U.S.C. 103 is a question of law.

Moreover, the Examiner is urged to appreciate that:

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (CAFC 1992).

Rather, an analysis of non obviousness must be based on several factual inquiries: (1) the scope and content of prior art; (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art at the time the invention was made, and (4) objective evidence of non obviousness, if any. *Graham v. John Deere Co*, 383 U.S. 1, 17 18, 148 USPQ 459, 467 (1966).

(1a) The scope and content of prior art leading up to the date of the invention:

To put the invention in the context of the prior art, it is necessary to consider not just the combination of documents (selected *ex post facto*) by the Examiner, but also other documents concerned with effector functions (e.g. FcR binding; ability to trigger complement and ADCC) and the regions of the IgG which trigger these.

A selection in chronological order:

Duncan and Winter (1988. Nature, 332: 738 – 740) (attached and listed on the attached PTO 1449 Form).

This work is still much cited (for example, by the articles marked * in the following) and used scanning mutations of surface residues of murine IgG2b. The ability to lyse NIP-coated sheep RBC in the presence of guinea pig complement was found to depend on the presence of certain residues at positions 297 (i.e. presence of carbohydrate), 318, 320 and 322. Interestingly, the mutation P331G was amongst others tested which had no effect.

Tao et al. (1991. J Exp Med, 173: 1025 – 1028 *).

These workers used guinea pig complement and haptenated sheep red blood cells under conditions where IgG2 was totally inactive. Domain swaps between active IgG3 and inactive IgG2 suggested the CH2 domain as being responsible for the differences in activity between the two antibodies. A second set of experiments used antibodies with hybrid IgG1 and IgG4 constant regions and showed that sequences of IgG1 permitting complement fixation were located mainly in the second half of the CH2 and/or CH3 domain although the first half of the IgG1 constant region was actually three-fold more effective than that of IgG4.

Valim and Lachmann (1991. Clin Exp Immunol, 84: 1 – 8) (attached and listed on the attached PTO 1449 Form).

This article highlighted that many different factors may affect the ability of a given human immunoglobulin to fix human complement. The conclusions were that activation is generally greatest at high epitope density and in conditions of antibody excess or antibody/antigen equivalence and that conditions suitable for activation of the classical pathway do not always allow activation via the alternative pathway.

Sarmay et al. (1992. Mol Immunol, 29: 633 – 639) (attached and listed on the attached PTO 1449 Form).

This document was concerned with the interaction between the lower hinge region and FcRs. The paper examined the effects of point mutations at residues 234, 235, 236 or 237 or aglycosylation on the activity of IgG3 in rosetting and ADCC assays using either cell lines stimulated to express mainly FcγRI or FcγRII or human K cells expressing FcγRIII. Although (with the possible exception of that at 236) these changes did appear to reduce this activity (the level of reduction varying with mutation and with cell type), the article paints a confused picture. The relative levels of FcγRI and FcγRII on the cell lines and their contributions to the assays are unclear, plus there was little correlation between the abilities to form rosettes and mediate ADCC.

Michaelsen et al. (1992. Mol Immunol, 29: 319 – 326 *) (attached and listed on the attached PTO 1449 Form).

This paper states that "complement-mediated lysis and ADCC have different structural requirements in the Fc region of IgG." (p319), based on their examination of IgG3 hinge mutants. Stepwise reduction of hinge length from 62 to 15 residues, to

resemble the hinges of other subclasses, or mutation to be identical to the IgG4 hinge had no effect on ADCC activity with NK/K cells. Complete removal of the hinge reduced ADCC by 100-fold but did not eliminate it. In contrast, complement-mediated lysis was enhanced with the 15 residue hinge and eliminated by complete removal. Epitope patchiness increased complement-mediated lysis but reduced ADCC.

Dorai et al. (1992. Mol Immunol, 29: 1487 – 1491 *) (attached and listed on the attached PTO 1449 Form).

This paper showed that the inter-heavy and light chain disulphide bond pattern also affects complement- and FcR-mediated effector functions. The IgG1 heavy chain is unique in forming a disulphide bond with the light chain from a position in the hinge rather than from a point at the N-terminal end of the CH1 domain. When IgG1 was mutated to have the same disulphide bond arrangement as IgG4, its ability to mediate ADCC by human PBMC was effectively abolished, falling at least 10^6-fold to be less than that of IgG4, and it was 10-fold less efficient at mediating complement-dependent lysis. The authors note that similar properties resulted from the removal of the inter-heavy chain disulphide bond.

Wright and Morrison (1994. J Exp Med, 180: 1087 – 1096 *) (attached and listed on the attached PTO 1449 Form).

These authors investigated the effect of changing the nature of the carbohydrate rather than its complete removal. They compared of the activities of IgG1 antibodies produced from wildtype CHO cells and CHO cell line Lec 1, which synthesizes oligomannosyl, truncated sugars not normally found on IgG. Lysis and consumption of guinea pig **complement** was reduced at least 10-fold and binding of human C1q was

decreased by altering the carbohydrate. Binding to human FcγRI was reduced about five-fold.

Brekke et al. (1995, Immunol Today, 16: 85 – 90 *) (attached and listed on the attached PTO 1449 Form).

This review notes that the hinge, and the flexibility it offers, are not in themselves essential for **complement activation** although they may assist in interaction with multiple antigen sites. However the inter-heavy chain disulphide bridge is necessary, although it still allows activity if repositioned from the hinge to the beginning of the lower hinge region of the CH2 domain.

The authors refer to Duncan & Winter (1988) and their attempt to locate the binding site for C1q on IgG by site-directed mutagenesis. They also note that work swapping sections of domains has shown the C-terminal part of the CH2 domain to be important and that residue 331 is partly, **but only partly**, responsible for the difference between human IgG1 and IgG4.

When non-lytic murine IgG1 was substituted with the lower region or with three individual hinge-proximal loops from lytic IgG2b, the lytic activity was not transferred to it.

On this subject, they finish by stating "Clearly, more work is needed to elucidate which additional residues in the CH2 domain are involved in complement activation." (p 88).

Ward and Ghetie (1995. Therapeutic Immunology, 2: 77 – 94 *) (attached and listed on the attached PTO 1449 Form).

This discusses a similar set of factors affecting ability to mediate complement lysis as that covered by Brekke et al.(1995) but also points *inter alia* to residue **237** of the lower hinge region. On the subject of activity via Fc receptors, the authors look at the importance of the lower hinge region (residues 233 - 238) and discuss different mutations in the region which have affected receptor binding. They conclude that this site is recognized by all three classes of FcγR but in a different way such that different residues are important for different receptors.

A E**318**A change in murine IgG2b removed its ability to form rosettes via FcγRII. The authors state that "It is obvious that there are not enough data to claim that the FcγR-binding region of IgG is located in three distinct regions irrespective of the class of FcγR recognized." (p83), indicating that the residues involved in the binding have not been elucidated for all three classes of FcγR. A glycosylation also reduces binding to FcγR. In concluding, the authors say "...there is evidence that three sequentially distinct, but spatially close peptide stretches are involved in building both C1q and FcR interaction sites." and "...it will be difficult to genetically engineer an IgG antibody to abolish complement activation whilst retaining FcγR binding." (p 90).

(1b) The scope and content of the art cited in the final rejection

The disclosure of each of cited documents was discussed in the applicants' previous response and, for economy, will not be repeated here. However the Examiner has reiterated the objections over the 4 prior art documents Greenwood, Morgan, Chappel & Cole.

In fact, even at a purely technical level, the applicants believe that the final rejection does not accurately depict the disclosure of the 4 prior art documents relied

upon, in terms of the results obtained by these earlier workers and the manner in which they were presented. Referring to the final rejection:

Greenwood

Paper No. 22, Page 20 Lines 14-15 & page 21 Lines 7-8: The hinge-link (or lower hinge) region is residues 231 – 238 (see present application, page 4, line 32) which is not in the C-terminal half of the CH2 domain.

Referring to page 1099, column 1, paragraph 1, lines 9 onwards, this is a discussion about what may have been thought **previously** about sites for FcγRI and FcγRIII binding, However Greenwood et al. actually **teach away** from the hinge link being an area of interest, instead focussing on the C-terminal half (discussion of their results starting "However..."). Their own results do not suggest any role for the hinge-link region in ADCC/complement lysis.

Paper No. 22, Page 20 Lines 26-27: The examiner refers, repeatedly, to "the reference binding molecule" having some structure e.g. Ala235. However none of Greenwood's **mutants** contain A235, and none of the **wild-type** molecules are pertinent to the present claims. The Examiner is believed to be intermixing the disclosure of the mutants and wild-type immunoglobulins under the umbrella term "the reference binding molecule", but this is not what the document discloses, and the Examiner's attempt to base a rejection on other than what a teaching discloses is inappropriate and must involve an impermissible use of hindsight.

Paper No. 22, Page 21 Lines 6-7 & Line 9-11: Greenwood teaches that all human IgG subclasses can mediate ADCC in some individuals, not that IgG2 and IgG4

are ineffective. The 'ineffective' is a quote of previous results, and is expressly contradicted by Greenwood itself (see Abstract, last 4 lines; also Introduction, last line).

Primarily Greenwood is concerned with the opposite aim of the presently claimed invention – namely increasing lytic activity. They attempt to locate the sites responsible for ADCC/complement lysis, and suggest that if multiple copies of the important regions were incorporated into a recombinant antibody then the effector activity might be increased (although no evidence is presented for this).

Interestingly, in terms of blockading target cells (as in the present invention), Greenwood et al. advocate native IgG4 (see page 1099, last sentence of Introduction). There is no discussion of whether or indeed how it could be improved for this purpose. The Examiner's comments in respect of improving effector functions by mutants which lack ADCC etc. (Page 25 Line 23-27) are not supported by the document.

The Examiner is respectfully reminded:

"It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965).

The following comments are further offered for completeness:

Paper No. 20, Page 20 Line 24: the Examiner's discussion of 98% identity with wild type CH2 is submitted to be incorrect (4 changes in 110 residues is less than 98% identity) and irrelevant (since the reference point with claim 41 is a CH2 including the mutations e.g. as judged against G1Δab, G1Δac, G4Δc, or G2Δa).

In respect of the Examiner's comment at Page 25 Lines 31-32, irrespective of the word "has", none of the Greenwood molecules contain 233P, 234V or 235A – hence the presently claimed invention does not read on to Greenwood, as apparently confirmed by the Examiner's apparent acknowledgement that the claims are novel over Greenwood.

Paper No. 22, Page 21 Lines 11-12 : the applicants note that "donor heterogeneity" is neither a therapy nor a condition requiring therapy but rather an observation that cells from different donors are able to give ADCC to different extents with some subclasses of human IgG. Accordingly, the applicants are unable to understand the point the Examiner is making and clarification is requested in the event any rejection or objection is maintained based on the same.

Morgan

Page 22, Page 22 Lines 10-17& 18-19; Page 24 Lines 4-5: Examiner has selected G1 [L235A] from Morgan since this change, though in effect Ala scanning, coincidently introduces the IgG2 residue.

However the Examiner appears to have misinterpreted Table 2, page 321. In this Table lower numbers represent more active antibodies. Hence G1 [L235A] shows very high levels of ADCC (tight RIII binding) and (compared to other mutants and IgG2 and 4) measurable FcγRI binding. These results would thus teach away from this mutation in trying to solve the problem addressed by the present invention.

Indeed, considering the IgG1 mutants of Morgan, the testing of "G1/G2L-hinge" showed it to be quite active in ADCC. G1[L235A] shows some FcγRI binding and both it and G1[L235E] exhibit high ADCC (indeed, based on Table 2 alone, it seems that

[L235E] would be preferred at least to [L235A] – but the former does not form part of the present invention). Another lower hinge mutant, G1[G237A], shows ADCC equal to IgG4 and significant complement lysis activity. Thus, none of the IgG1 mutants lack all three measured functions.

The Examiner also appears to be confusing FcγRI and FcRn receptor. In the presently claimed invention binding to the former is to be avoided while the latter is retained.

Chappel

Paper No. 22, Page 23 Line 1 onwards: The Examiner has highlighted IgG2-2-1-2 from Chappel, again seemingly assuming that FcγRI binding is a part of the presently claimed invention. Although the Examiner again refers to "the reference binding molecule" it is again not clear which one of Chappel's mutants this is. Clarification is requested.

In any case, none of the mutants matched those of the present claims, and since FcγRI was the only effector property (and this in an insensitive assay – see below), it cannot easily be deduced what effects on this or any other "effector function" were shown by the mutants (cf. action page 23 Line 15; Page 24, line 16).

Interestingly, the Chappel results suggest that IgG4 binds to FcγRI approximately 100-fold less efficiently than IgG1, whereas values in the literature vary from 2.5- to 20-fold (see also Figure 3 of the present specification, which shows a 2-3 fold difference). Indeed, the binding of IgG4 is on the edge of detection in the system used by Chappel (see Table 2 – value $0.04 \times 10^{8}\ M^{-1}$, note the table is seemingly in error in stating $10^{-8}\ M^{-1}$) so that any change causing an antibody to bind even slightly less than IgG4 to

FcγRI would be classed as 'completely abolishing cytophilic activity'. The binding data in Chappel must therefore be viewed with caution.

In any case, even though (for example) in the IgG1 competitive assay results in Figure 4a, many mutants (including IgG1 containing an IgG2 point mutation – 'PLLGGP') are shown as having binding tighter than or commensurate with IgG4, no apparent Ka values are even listed for these in Table 2. There seems to be no reason for this. Therefore the question of whether even these point mutants had "abolished cytophilic activity" seems unanswered on the basis of the data (cf. action page 26 Line 30-32.)

Cole

Paper No. 22, Page 23 Line 22, Page 25 Lines 21-27, Page 26, line 15 to Page 27, line 7. The Examiner has erred in stating that Cole "modified" modified residues to give V234 and A235 in IgG2 – these are the natural IgG2 residues, and the applicants refer again to the underlined residues in Table 1, page 3615. The Examiner's misconception on this point has been repeatedly drawn to the Examiner's attention – first in the applicants response filed on April 8, 2002, pages 6; then in the applicants' previous response page 10.

Paper No. 22, Page 23 Line 23: Binding to FcγRIIb is not measured. The Examiner's assertion, repeated in all actions to date, is therefore unsupported by the evidence (see discussion in response filed on April 8, 2002, pages 4-5, including reference to Warmerdam papers of record).

Paper No. 22, Page 23 Line 26-27: As noted by the examiner, Cole teaches mutating IgG2 in the lower hinge region (e.g. making unnatural mutations at 234). The

point mutation of the IgG2 lower hinge apparently produced CD3 antibody mutants that caused less T-cell proliferation and cytokine release than wildtype human IgG of all four subclasses and a IgG4 lower hinge mutant.

Indeed, based on the comments of Examiner, it seems that [Ala234] would be a desirable mutation to introduce – however this does not form part of the presently claimed invention.

(1c) Conclusions on the art

By reviewing the art, as one of ordinary skill in the art, without benefit of the applicants' disclosure, several issues become apparent. Sometimes-contradictory evidence obtained using numerous different systems and focusing on numerous different possible regions meant that it was not possible to draw general conclusions about effector functions, and IgG constant regions. Indeed, given the complications highlighted by Valim & Lachmann, it is not surprising that groups testing the effects of mutations on complement activity have obtained different results, especially since not all have utilized human complement. To take one example, Brekke et al. suggested glycosylation of the CH2 domains was crucial for activation, and the presence of the CH3 domains was also essential for full activity. However even this apparently straight-forward conclusion is complicated by the fact that the ability to bind to C1q was not sufficient for complement activation, since other factors appeared to discriminate between subclasses at the level of complement component C4.

Thus, the applicants submit that it was unclear at the date of invention whether point mutations of the CH2 domain could even be used to finely tune the interactions

between IgGs and effector molecules. Even if a point mutation approach was adopted, it was not clear which were the residues to mutate and which amino acids to substitute.

(2) The differences between the prior art and the claims at issue

All the present claims are based on natural IgG1,2 or 4 CH2 regions in which mutations, only taken from other IgG sub-classes, have been introduced such as to give specific amino acids at positions the lower hinge region 233-236 (the so-called Δb or Δc mutations corresponding to IgG2) and 327, 330-1 (the so-called Δa mutation corresponding to IgG4).

The molecules of the claims are capable of binding the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, and capable of specifically binding FcγRIIb and optionally FcRn – as evidenced by Figures 1 to 14 and Examples 1 to 6b. As discussed in more detail in section 4 below these molecules have improved effector functions even with respect to any of the progenitor immunoglobulins.

Despite the inference from Ward & Ghettie, the present invention has shown that it is possible to retain binding to one form of FcγR (FcγRIIb) while greatly reducing complement activation. Moreover, the present inventors used as a test system (for complement lysis) the antigen CAMPATH-1 on human cells and human serum in which even IgG2 to exhibited strong lytic activity (cf. Tao et al. 1991, and other workers who used systems in which IgG2 was itself inactive). Thus it is highly likely that any antibody variants that are not active in the system of the present inventors would also be inactivate under conditions which were less conducive to lysis.

The differences between the cited prior art and the claims are apparent from the discussion above.

Notably, the Examiner (Page 21, Line 14 onwards in Paper No. 22) has not accurately presented the differences between the claimed invention and Greenwood. The inventions of claim 32 etc. differ from the teachings of Greenwood functionally. Whereas Greenwood only considered complement lysis and ADCC, the application presents data for binding to three classes of FcγR and the activation of monocytes. Retained binding to FcγRIIb (and optionally FcRn) are also feature of the claims are not "taught" by Greenwood. Indeed this seems to be acknowledged by the Examiner (see, Page 22, Lines 7-8 of Paper No. 22). Additionally, the Examiner has inaccurately stated the sequence differences between any individual mutant provided by Greenwood, and the presently claimed molecules (see above comments on "the reference binding molecule").

To summarize, the applicants submit that Greenwood is concerned with the opposite aim of the present invention – namely increasing lytic activity. In terms of blockading target cells (as in the present invention) they advocate native IgG4. This is a fundamentally different solution to that defined in the present claims.

Morgan does not encourage the reader to consider lower hinge mutations as a route to a non-destructive antibody. None of their IgG1 molecules, carrying either point mutations in the lower hinge or the block of IgG2 residues, reduced FcγRI binding, ADCC and complement activities.

Chappel shows only that point mutation of the lower hinge can reduce the FcγRI binding of IgG1 but not to what extent.

Cole might look to be more successful, producing a mutant which does not activate T cells and which has been shown not to bind to FcγRI or FcγRIIa (although its efficiencies in ADCC and complement lysis were not assessed). However Cole's method was to introduce unnatural residues into the lower hinge of IgG2, whereas the present claims require the relevant residues of the binding molecule to correspond to native IgG2.

(3) The level of ordinary skill in the art at the time the invention was made

This is discussed above in respect of the *Wands* factors. In terms of the ability to prepare and test mutants for different activities the skill is in principle high.

However one of ordinary skill in the art can only follow the teaching of the art. Even if deficiencies or uncertainty in that art are apparent, any modification must be, by definition, conservative and non-inventive, and consonant with the direction of the art. As stated in *Woodstream Corp. v. Herter's, Inc.*, 170 USPQ 380, 387 (8th Cir. 1971):

"[W]hile the deficiencies in the prior art were readily recognizable, it does not follow that the solution to those problems would have been obvious to one possessing ordinary skill in the art."

For example, Morgan made four IgG1 molecules with mutations in the lower hinge region. These mutations had different effects on the three functions tested but none of the mutants was negative for all three functions. An objective reading of this document by the ordinarily skilled person would not have directed him towards the presently claimed invention in which the specified effector functions have been reduced or retained according to the mutations directed in the present claims.

Even if the ordinarily skilled person departed from Greenwood's teaching to use IgG4 and decided, for some reason, to construct a simple inert IgG based on these papers, the ordinarily skilled person would arguably have been directed to actually mutate the IgG2 lower hinge (c.f. Cole, or 235E in Morgan). Indeed, although noting the ability of IgG2 in complement activation was particularly dependent on epitope density and antibody/antigen ratios, arguably the Valim & Lachmann paper emphasizes the ability of IgG2 to trigger complement (via both of the complement pathways).

The cited art fails to provide motivation to make the presently claimed invention, with a reasonable expectation of success. The Section 103 rejections of the claims should be withdrawn. The Examiner is urged to appreciate that:

"The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification" *In re Gordon*, 221 USPQ 1125, 1127 (CAFC 1984).

Indeed, as a question of historical fact, other workers at the priority date, trying to achieve some of the same effector functions (admittedly not all them) chose quite different residues and substitutions. See discussion of Genentech's (WO 99/51642 & US 6,194,551 – copies submitted with attached Information Disclosure Statement) which focuses on quite different CH2 positions (270 & 329).

The applicants submit therefore that a fair reading of the documents, without hindsight knowledge of the present invention, shows that even if the ordinarily skilled person was starting with one or more of the 4 cited references to try and achieve the aims of the presently claimed invention, these documents or any reasonable combination thereof would not have directed the person of ordinary skill in the art to

which regions to modify (and which regions not to modify), and which residues to introduce there, in order to achieve the solution set out in the present claims.

(4) Objective evidence of non obviousness,

Unexpected results

Even if the ordinarily skilled person had an idea about which regions to modify and how to do it to, they would not have "reasonably expected" that multiple effector functions could reconciled in the manner achieved by the present invention. The position that the Examiner has taken is that it was believed in the art that the effector functions can simply be independently manipulated and combined in any IgG background by simple substitutions. However this position is not supported by the literature of record.

Considering the present application, in respect of FcγRI binding, Figures 2 and 3 show that mutations Δb and Δc of IgG1 (+/- Δa) and IgG4 produced mutants with very low or undetectable binding to this receptor. The binding was at least 1000-fold lower than that of IgG4 - a result could scarcely have been predicted from Chappel where the binding of wild-type IgG4 itself was practically undetectable.

The activation of monocytes in response to antibody-sensitised RBC is zero when using IgG2 or several of the mutant IgG including G1Δb and G2Δa (Figure 4). However, in experiments where the inactive antibodies were used to try to inhibit the activity of IgG1, IgG2 was four-fold less efficient than the mutant antibodies (Figure 5).

Figure 10a shows an example of ADCC where IgG2 and IgG4 mediate significant levels of lysis. Substitution of IgG2 residues into IgG4 (G4Δb), IgG4 residues into IgG2 (G2Δa) or both IgG2 and IgG4 residues into IgG1 (G1Δab) effectively eliminates killing.

The activity of these mutants is at least 100-fold less than that of IgG2 and IgG4 and they are more effective than IgG2 and IgG4 in blocking the activity of active antibody (Figures 11a and 12).

In binding to FcγRIIa 131H (Figure 13a), IgG1 and IgG2 are equally active. Taking residues from the inactive IgG4 and substituting them into IgG1 and IgG2 (G1Δa and G2Δa) reduces binding by about four-fold. However taking residues from the active IgG2 and substituting them into IgG1 reduces binding by factors of 10 (G1Δc) or 50 (G1Δb).

Thus the present inventors showed, inter alia:

That IgG mutants with less effector activity than either of the parent antibodies could be created (see above) and indeed that substitutions from an "active" subclass could be more efficient at reducing activity than those from an inactive subclass (see e.g. Figure 7, which shows that G1Δb and G1Δc, derived from the active IgG2, nevertheless reduced complement activity in IgG1 to background levels and thus were more effective than the Δa change, based on the inactive IgG4).

That a relatively high level of binding to FcγRIIb could be retained whilst effecting a much greater reduction in binding to FcγRIIa, notwithstanding that the receptors are so similar in structure.

In view of the foregoing, it is clearly improper to simply assert that there was a "reasonable expectation" of arriving at the invention. Rather it is necessary under Section 103 to demonstrate some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to

combine the relevant teachings of the references to produce the claimed invention. Absent such teaching or knowledge, inventive step must be acknowledged.

The claims are submitted to be patentable over the art of record. The Examiner has failed to establish a *prima facie* case of obviousness. The Section 103 rejections should be withdrawn.

A Notice of Allowance is requested. As noted above, an Examiner interview is requested prior to the Examiner mailing a further substantive Action, in the event there are any outstanding objections and/or rejections or in the event the Rule 181 Petition is not decided favorably.

Respectfully submitted,

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ABSTRACT

Disclosed are binding molecules which are recombinant polypeptides containing: (i) a binding domain capable of binding a target molecule, and (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain; characterized in that the binding molecule is capable of binding the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, and more preferably wherein the effector domain is capable of specifically binding FcRn and/or FcγRIIb. These are generally based on chimeric domains which are derived from two or more human immunoglobulin heavy chain CH2 domains domains. In preferred embodiments the regions 233-236, and 327-331, are modified, as are further residues to render the molecule null allotypic. Also disclosed are nucleic acids, host cells, production processes and materials, and uses. Pharmaceutical preparations are also disclosed.